SEARCH FOR ISOFORM-SPECIFIC INHIBITORS OF CASEIN KINASE 1 USING COMPUTATIONAL TOOLS

Emmanuel Orfanakis[*], Ifigeneia Akrani[*], Haralambos Katerinopoulos[**], Vassilios Myrianthopoulos[*] and Emmanuel Mikros[*]

[*] Division of Pharmaceutical Chemistry, School of Pharmacy, National and Kapodistrian University of Athens, Panepistimiopolis Zografou, 157 71, Athens, Greece.
[**] Division of Organic Chemistry, Department of Chemistry, University of Crete, 700 13, Heraklion, Crete, Greece.

In recent years, there has been widespread use of computer methodologies in search of new drugs by rational approaches. Particularly, the field of small molecule inhibitors targeting disease-relevant kinases has greatly profited by such tools. In the present study, efforts for identifying and evaluating molecules with potential inhibitory activities against the group of Casein Kinase 1 (CK1) isoforms are presented. The CK1 subfamily comprises seven isoforms which are regarded as promising pharmacological targets for treating various pathologies. These protein kinases phosphorylate serine-threonine residues and differ significantly from Casein Kinase 2. Several CK1 isoforms have been found to be frequently deregulated in many types of cancer, inflammatory diseases as well as in various neurodegenerative disorders.

A computational search of CK1 inhibitors was performed in four highly diverse, open-access compound collections from NCI, the Diversity, Mechanistic, Approved Oncology and Natural Products sets. Three different and orthogonal computational algorithms including docking-scoring calculations, two-dimensional fingerprint similarity and three-dimensional shape-pharmacophore similarity were used for virtually evaluating the compounds with respect to their binding properties for CK1 isoforms alpha, gamma, delta and epsilon. First, a theoretical model was constructed and validated by the use of experimentally available binding affinities. Subsequently, both structure-based and ligand-based computational tools were independently applied for prioritizing potential hit compounds. Finally, results obtained through the different abovementioned techniques were further consensus-ranked and a group of molecules with high probabilities of being biologically active were selected. The binding geometries and modes of interaction between these potential hits and the target kinases were thoroughly studied by Molecular dynamics simulations to extract notions of structure-activity relationships and guide their experimental activity assessment and potential optimization. Emphasis was paid to the computational identification of structural features related to isoform-selective inhibition of CK1. Compounds that exhibit optimal predicted pharmacokinetic characteristics, selectivity and high anticipated kinase inhibitory activities will be tested experimentally as potential inhibitors of the aforementioned proteins.